Amendments to the Specification

On p. 1 and elsewhere, please amend the title of the application as follows:

Methods for evaluating the ability to metabolize pharmaceuticals ~~and compositions therefor~~

On p. 1, please amend the first sentence of the specification as indicated in the marked up replacement paragraph shown below:

REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part application of U.S. Patent application Serial No. 09/144,367, filed August 31, 1998, now Patent No. 6,432,639, which is hereby incorporated by reference in its entirety. This application claims the benefit of Provisional Patent Application Serial No. 60/271,630 filed in the U.S. Patent and Trademark Office on February 26, 2001, which is hereby incorporated by reference in its entirety.

In the last paragraph of p. 25, please amend the specification as shown below in the marked up replacement below:

Blood specimens from 32 individuals were collected after obtaining informed consent. All samples were stripped of personal identifiers to maintain confidentiality. The only data associated with the sample were self-reported gender and racial group designations. Of the 32 individuals, 10 were African Americans, 10 were Caucasians, 6 were Japanese and 6 were Chinese. Genomic DNA was isolated using standard methods. Polymerase chain reaction (PCR) amplification of regions of the CYP4503A5 gene were performed using the primers listed in Table 2. The PCR amplification was performed in a total reaction volume of 50 microliters (μl). The final magnesium chloride concentration (2mM) was optimized empirically. The final genomic DNA concentration was about 100 nanogram (ng) per reaction from 2 individuals. The PCR reactions were performed using Perkin Elmer ~~GeneAmp~~ GENEAMP® PCR kit (available from Perkin Elmer, Norwalk, CN) using Taq Gold DNA polymerase according to manufacturer's instructions

On p. 26 in the specification, please amend the following paragraph as indicated in the marked up replacement paragraph below:

The resulting PCR products were purified using ~~Microcon~~MICROCON®-100 columns (available from Millipore, Bedford, MA). PCR products from two individuals were combined for each cycle of sequencing. Cycle sequencing was performed on the ~~GeneAmp~~ GENEAMP® PCR System 9600 PCR machine using the ABI ~~Prism~~ PRISM® dRhodamine Terminator Cycle Sequencing Ready Reaction Kit (available from Applied Biosystems, Inc., Foster City, CA) according to the manufacturer's directions. Oligonucleotide primers used for the sequencing reactions include those shown in Table 3.

On p. 28, please amend the following paragraph as indicated in the marked up replacement below:

Genomic DNA was isolated from peripheral blood lymphocytes of 86 chemotherapy naive female patients with metastatic or inflammatory breast cancer who participated in a trial for high-dose cyclophosphamide (CY), cisplatin and 1,3-bis-(chloroethyl)-1-nitrosourea (BCNU) chemotherapy with breast cancer using standard methods. DNA from each patient was genotyped for the Promoter –392 CYP4503A4 single nucleotide polymorphisms (SNPs) in the CYP3A4 gene. ~~Taqman~~ TAQMAN® assays were performed using DNA samples from each individual to identify the presence or absence of the Promoter -392 CYP4503A4 variant. The primers identified in Table 5 were used:

On p. 28 bridging to p. 29, please amend the following paragraph as indicated in the marked up replacement below:

PCR amplification was performed using 1X Perkin-Elmer TAQMAN® ~~Taqman~~ Reagent Mix #43C4447, about 900 nM 3A4-392 for primer, about 900 nM 3A4-392 rev primer, about 200 nM normal FAM™-labeled probe having the nucleic acid sequence 5'-AGAGACAAGGGCAAGAGAGAGGCGAT-3' (SEQ ID NO:19), and 200 nM variant TET™-labeled probe having the nucleic acid sequence 5'-GACAAGGGCAGGAGAGAGGCGA-3' (SEQ ID NO:20). Thermal cycling was performed at an initial temperature of 50°C for 2 min followed by a denaturation step at 95°C for 10 min, followed by 40 cycles of denaturation at 94°C for 30 sec, primer annealing and extension was performed at 60°C 30 sec. The fluorescence resulting from the release of labeled probe during PCR amplification and probe hybridization was measured using a fluorometer and the ratio of FAM™ to TET™ fluorescence was calculated to determine the occurrence of the polymorphic site and homo- or heterozygosity compared to sequenced controls.

On p. 31, please amend the following paragraphs as indicated in the marked up replacements below:

The genomic DNA described above in Example 2 was genotyped for the Promoter -147 CYP4503A5 single nucleotide polymorphisms (SNPs) in the CYP3A5 gene. TAQMAN® ~~Taqman~~ assays were performed using DNA samples from each individual to identify the presence or absence of the Promoter -147 CYP4503A5 variant. The primers described in Table 7 were used:

PCR amplification was performed using 1X Perkin-Elmer TAQMAN® ~~Taqman~~ Reagent Mix #43C444 7 with about 900 nM 3A5-147 for primer, about 900 nM 3A5-147 rev primer, about 150 nM FAM™-labeled probe having the nucleic acid sequence 5'-CTGCAGCCCCACCTCCTTCTCC-3' (SEQ ID NO:23) and 250 nM variant VIC®-labeled probe having the nucleic acid sequence 5'-CTGCAGCCCCGCCTCCTTCTC-3' (SEQ ID NO:24). Thermal cycling was performed with at initial temperature of 50°C for 2 min for activation of the ~~Amperase~~ AMPERASE® UNG in the TAQMAN® ~~Taqman~~ Reagent Mix followed by a denaturation step at 95°C for 10 min, followed by 40 cycles of denaturation at 60°C for 30 sec, primer annealing and extension was performed at 60°C for 30sec. The fluorescence resulting from the release of probe labels during PCR and probe hybridization was measured using a fluorometer and the ratio of FAM™ to VIC® fluorescence was calculated

On p. 34, please amend the following table and paragraph as indicated in the marked up replacement paragraph below:

Table 9. PCR Primers

PCR Primer	SEQ ID NO:	Primer Sequence
GSTM1-null forward	~~23~~27	GAACTCCCTGAAAAGCTAAAGC
GSTM1-control forward	~~24~~28	GAACTGCCACTTCAGCTGTCT
GSTM1-null reverse	25	GTTGGGCTCAAATATACGGTGG
GSTM1-control reverse	26	CAGCTGCATTTGGAAGTGCTC

PCR amplification was performed at a $MgCl_2$ concentration of 2.5 mM in 1 X buffer D (33.5 mM Tris-HCl, pH 8, 8.3 mM $(NH_4)_2SO_4$, 25 mM KCl and 0.085 mg/ml BSA) with 1.25 mM dNTPs, and 0.05 U/µl Perkin Elmer ~~AmpliTaq~~ AMPLITAQ® Gold polymerase. The following primers were used in the PCR reaction: about 300 nM TET™-labeled GSTM1-null for primer, about 300 nM unlabeled GSTM1-null rev primer, about 300 nM HEX™-labeled GSTM1-control for primer and about 300 nM unlabeled GSTM1-control rev primer. Thermal cycling was performed with an initial denaturation step at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 2 min, primer annealing at 59°C for 1 min and extension at 72°C for 1 min, followed by 10 min at 72°C. The resulting PCR products were resolved using standard acrylamide gel electrophoresis methods. The flourescence emitted from the GSTM1 PCR products and the control PCR products were compared using ABI ~~Prism~~ PRISM® ~~GeneScan~~ GENESCAN® 2.1 software (available from ABI).